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CLINICAL TRIALS AND OBSERVATIONS

Recombinant *Erwinia* asparaginase (JZP458) in acute lymphoblastic leukemia: results from the phase 2/3 AALL1931 study

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KEY POINTS

- **Intramuscular JZP458 at 25/25/50 mg/m^2 M/W/F was effective in patients with ALL/LBL, with a safety profile similar to other asparaginases.**
- **JZP458 overcomes one of the most significant drug shortage issues facing patients with ALL/LBL.**

AALL1931, a phase 2/3 study conducted in collaboration with the Children's Oncology Group, investigated the efficacy and safety of JZP458 (asparaginase erwinia chrysanthemi [recombinant]-rywn), a recombinant *Erwinia* asparaginase derived from a novel expression platform, in patients with acute lymphoblastic leukemia/lymphoblastic lymphoma who developed hypersensitivity/silent inactivation to *Escherichia coli*–derived asparaginases. Each dose of a pegylated *E coli*–derived asparaginase remaining in patients' treatment plan was substituted by 6 doses of intramuscular (IM) JZP458 on Monday/Wednesday/Friday (MWF). Three regimens were evaluated: cohort 1a, 25 mg/m^2 MWF; cohort 1b, 37.5 mg/m^2 MWF; and cohort 1c, 25/25/50 mg/m^2 MWF. Efficacy was evaluated by the proportion of patients maintaining adequate nadir serum asparaginase activity (NSAA ≥0.1 IU/mL) at 72 hours and at 48 hours during the first treatment course. A total of 167 patients were enrolled: cohort 1a (n = 33), cohort 1b (n = 83), and cohort 1c (n = 51). Mean serum asparaginase activity levels (IU/mL) at 72 hours were cohort 1a, 0.16, cohort 1b, 0.33, and cohort 1c, 0.47, and at 48 hours were 0.45, 0.88, and 0.66, respectively. The proportion of patients achieving NSAA ≥0.1 IU/mL at 72 and 48 hours in cohort 1c was 90% (44/49) and 96% (47/49), respectively. Simulated data from a population pharmacokinetic model matched the observed data well. Grade 3/4 treatment-related adverse events occurred in 86 of 167 (51%) patients; those leading to discontinuation included pancreatitis (6%), allergic reactions (5%), increased alanine aminotransferase (1%), and hyperammonemia (1%). Results demonstrate that IM JZP458 at 25/25/50 mg/m^2 MWF is efficacious and has a safety profile consistent with other asparaginases. This trial was registered at www.clinicaltrials.gov as #NCT04145531.

Introduction

Asparaginases are proteins originating from bacteria employed in the treatment of acute lymphoblastic leukemia (ALL) and lymphoblastic lymphoma (LBL), and come with a high allergenic and immunogenic potential.[1] Hypersensitivity reactions, ranging from localized erythema to systemic anaphylaxis, are the most common dose-limiting adverse events (AEs), occurring in up to 30% of patients receiving *Escherichia coli*–derived L-asparaginases.[2] In addition, antibody development can lead to inactivation of L-asparaginase activity in the absence of clinical symptoms, termed silent inactivation,[2] which is monitored via measurement of serum asparaginase activity (SAA). An SAA level of ≥0.1 IU/mL correlates with complete asparagine depletion.[3] In the setting of a hypersensitivity reaction or silent inactivation to an *E coli*–derived asparaginase, it is recommended to switch patients to an asparaginase preparation with a distinct immunogenic profile, such as an *Erwinia chrysanthemi*–derived asparaginase.[3]

JZP458 is a recombinant *Erwinia* asparaginase with an identical amino acid sequence to native *Erwinia* asparaginase (Erwinaze/Erwinase) but is derived from a novel *Pseudomonas fluorescens* expression platform. JZP458 is expected to have minimal immunologic cross-reactivity to *E coli*–derived asparaginase preparations and has comparable in vitro activity to native *Erwinia*-derived asparaginase.[4-7]

In a phase 1 study in adult healthy volunteers, JZP458 was evaluated at a starting dose of 25 mg/m^2, chosen to provide similar asparaginase activity to native *Erwinia* asparaginase at 25 000 IU/m^2 based on in vitro analytical comparability. Results from that phase 1 study demonstrated that a single dose of 25 mg/m^2 intramuscular (IM) JZP458 resulted in similar SAA to 25 000 IU/m^2 of native *Erwinia* asparaginase.[4]

The AALL1931 study was initiated in patients with ALL or LBL and was conducted in collaboration with the Children's Oncology Group. On the basis of interim data from this trial, JZP458 (Rylaze; asparaginase erwinia chrysanthemi [recombinant]-rywn) was approved by the US Food and Drug Administration (FDA) in June 2021 for the treatment of ALL/LBL in patients aged ≥1 month who have developed hypersensitivity to *E coli*–derived asparaginase, following review under the Real-Time Oncology Review (RTOR) program.[8]

Herein, we report the efficacy and safety results from part A of AALL1931, which investigated the IM route of administration in patients with ALL or LBL who developed hypersensitivity or silent inactivation to *E coli*–derived asparaginases.

Materials and methods

Study design and treatment

AALL1931 (ClinicalTrials.gov identifier: NCT04145531) is a pivotal phase 2/3, open-label, multicenter, dose-confirmation, and pharmacokinetic (PK) study to assess the efficacy and safety of JZP458, designed to allow additional cohorts to be enrolled at a new dose following review of safety and efficacy results of the current cohort by the Study Data Review Committee (SDRC) during the dose-confirmation phase. Part A investigated the IM route of administration of JZP458, whereas part B (ongoing) investigated the intravenous route of administration. Each remaining pegylated *E coli*–derived asparaginase dose on a patient's treatment plan was replaced by 1 course of IM JZP458 (6 doses administered on a Monday/Wednesday/Friday [MWF] schedule over 2 weeks), with the initial dose starting on M, W, or F, to align with the patient's planned chemotherapy schedule. All other chemotherapy continued according to the original treatment protocol for the patient's ALL/LBL.

The starting dose for IM JZP458 was 25 mg/m^2 (cohort 1a) on MWF, based on data from the phase 1 study.[4] Subsequent to a review of cohort 1a nadir SAA (NSAA) and safety data by the SDRC, cohort 1b opened at 37.5 mg/m^2 on MWF. Population PK (PopPK) modeling and simulations were used throughout the conduct of the AALL1931 study to inform dosing decisions. After a preliminary PopPK model based on data from cohorts 1a and 1b predicted that a regimen of 25/25/50 mg/m^2 MWF would be required to achieve 72-hour NSAA levels ≥0.1 IU/mL to support MWF dosing, cohort 1c was initiated to evaluate this regimen.

Patients

Patients were enrolled in part A from December 2019 to March 2021 at ≈70 sites across North America. The study was conducted in accordance with Good Clinical Practice guidelines and the Declaration of Helsinki. All patients or their guardians (for patients aged <18 years) provided written informed consent and assent when indicated. The protocol and all amendments were approved by the institutional review board or ethics committee at each participating institution.

Pediatric or adult patients with newly diagnosed ALL/LBL were eligible if they developed a grade ≥3 allergic reaction (National Cancer Institute Common Terminology Criteria for Adverse Events version 5.0) to a pegylated *E coli*–derived asparaginase or silent inactivation (definition in supplemental Methods, available on the *Blood* website). Patients were considered ineligible if they had previously received native *Erwinia*-derived asparaginase or JZP458, had relapsed ALL/LBL, or a history of grade ≥3 pancreatitis. Full eligibility criteria are presented in the supplemental Methods.

Study end points and assessments

The primary efficacy end point of AALL1931 was the proportion of patients with the last 72-hour NSAA level ≥0.1 IU/mL (to evaluate SAA coverage from Friday to Monday), and the key secondary end point was the proportion of patients with the last 48-hour NSAA level ≥0.1 IU/mL (to evaluate SAA coverage from Monday to Wednesday or Wednesday to Friday, depending on the patient's scheduled starting day) during the first course of IM JZP458 administration. Additional secondary end points included the proportion of patients with the last 48- and 72-hour NSAA levels ≥0.4 IU/mL during the first course, characterization of the PK of IM JZP458 using a PopPK approach based on SAA, and assessment of immunogenicity following repeated administration.[9] Plasma asparagine concentration was included as an additional assessment.[9] Blood samples for SAA and asparagine were collected at prespecified time points (supplemental Table 1) and transferred on dry ice to bioanalytical laboratories. SAA samples were analyzed at Charles River Laboratories (Skokie, IL) using a validated enzyme activity assay in human serum over the range of 0.0349 to 0.2096 IU/mL. Asparagine samples were assayed for plasma asparagine concentration by Syneos Health (Princeton, NJ), using a validated liquid chromatography–tandem mass spectrometry method over the range of 0.025 to 10.0 µg/mL. Safety and tolerability were assessed by the occurrence of treatment-emergent AEs and treatment-related AEs. AEs were considered to be related to JZP458 if the event followed a reasonable temporal sequence from administration and satisfied ≥1 instances of clinical evidence: (1) the event followed a known or suspected response pattern to the study drug; (2) the event disappeared after stopping the study drug; or (3) the event reappeared after the study drug was restarted.

PopPK modeling and simulations

A PopPK model was developed for JZP458 with SAA data from AALL1931 using nonlinear mixed effects modeling (NONMEM; version 7.3) to describe the PK of JZP458 after IM administration. SAA was the basis of the PK assessment in this study.

The PopPK model included 2687 SAA data points from 166 patients who received IM JZP458 in this study: 32 patients from cohort 1a, 83 patients from cohort 1b, and 51 patients from cohort 1c. The effects of potential covariates were evaluated to identify the covariates likely to contribute to the variability of JZP458 PKs.

The model was used to simulate the SAA profiles for a virtual population with 2000 subjects (1000 pediatric and 1000 adult subjects) to explore the likelihood of achieving a therapeutic target NSAA level of ≥0.1 IU/mL based on different doses, schedules, and routes of administration. The virtual population ranged from 1 month to 80 years old to represent real-world scenarios. Dosing regimens tested in the AALL1931 study were simulated, and 1 dosing regimen not tested in the study was also simulated.

Statistical analysis

The primary and key secondary efficacy end points were assessed by calculating the 95% Wald confidence interval (CI) around the proportion of patients with NSAA levels ≥0.1 IU/mL. The efficacy analysis population included patients who received ≥1 dose of JZP458 and had at least one 48- or 72-hour NSAA assessment within the protocol-defined sample collection window (±2 hours) in the first course. The safety analysis population included patients who received ≥1 dose of JZP458. The PK analysis set included patients who received ≥1 dose of JZP458 and had ≥1 postdose evaluable SAA value.

Cohort determination

An interim analysis, including data from cohort 1a (25 mg/m^2 MWF) and cohort 1b (37.5 mg/m^2 MWF), was conducted by the SDRC after 51 patients in cohort 1b completed course 1. The SDRC recommended initiating cohort 1c based on the results of preliminary PopPK modeling and simulation while continuing enrollment in cohort 1b. Analysis of all patients enrolled in part A was conducted after 51 patients in cohort 1c (25/25/50 mg/m^2 MWF) completed course 1. This report uses data current as of July 19, 2021. Additional details are presented in the supplemental Methods.

Results

Patient characteristics and disposition

AALL1931 enrolled 167 patients to the 3 IM cohorts (cohort 1a, n = 33; cohort 1b, n = 83; and cohort 1c, n = 51). As of the cutoff date for this analysis, 27 (16%) patients were still receiving treatment, 104 (62%) patients had completed all planned doses of JZP458 treatment, and 36 (22%) patients had discontinued JZP458 treatment (Figure 1). The most common reason for

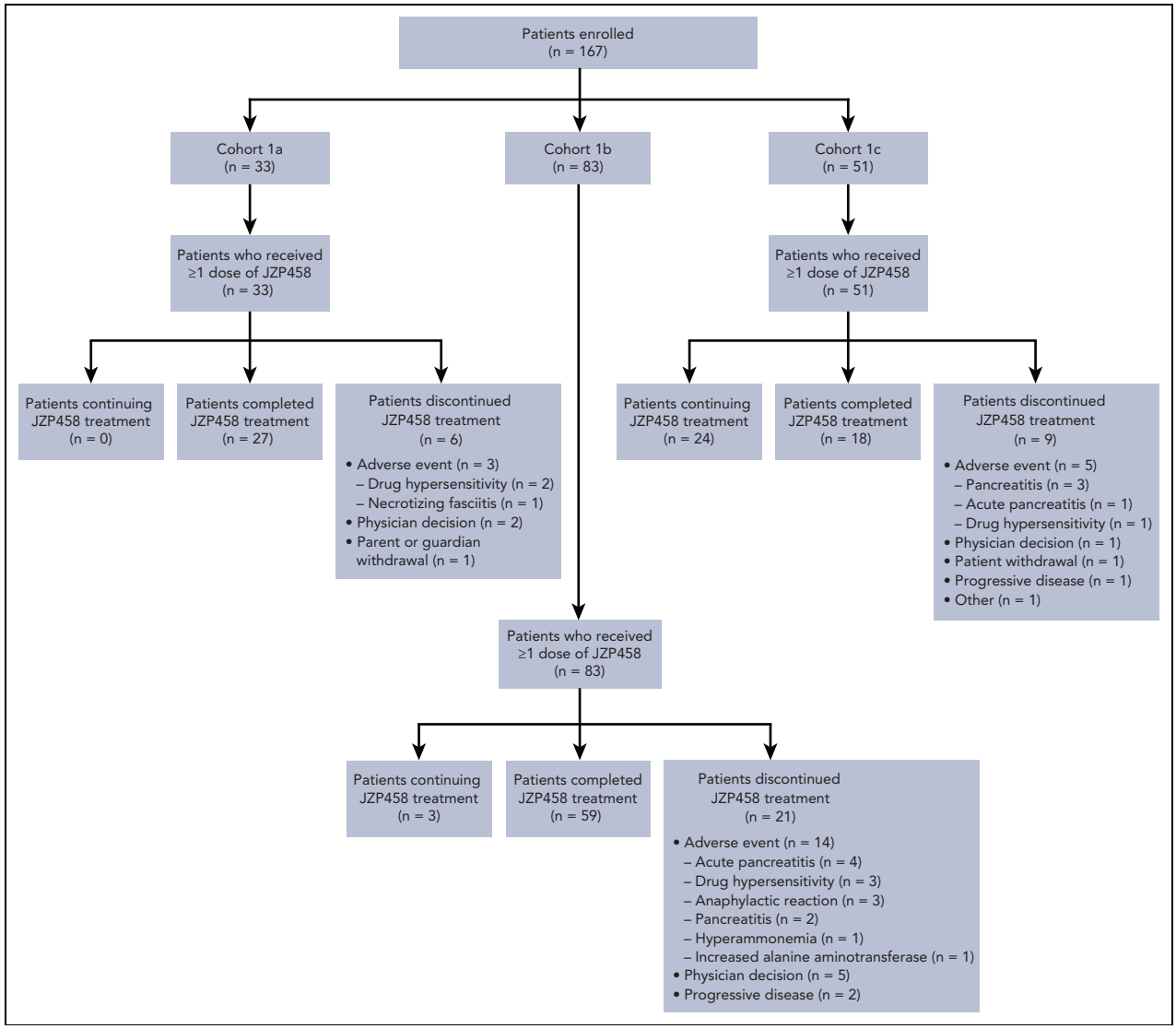

Figure 1. CONSORT diagram of patient disposition by cohort.

discontinuation was AEs (13% [n = 22]). The median (range) number of planned courses of JZP458 was 5 (1-14) for cohort 1a, 5 (1-15) for cohort 1b, and 5 (1-15) for cohort 1c. At the data cutoff date, the median (range) number of JZP458 courses received was 5 (1-14) for cohort 1a, 5 (1-15) for cohort 1b, and 4 (1-11) for cohort 1c (some patients were still receiving treatment).

Baseline demographic and disease characteristics are presented in Table 1. Median (range) age at enrollment was 10 (1-25) years, with 87% of patients aged <18 years.

Efficacy

Following the first treatment course of JZP458, the proportion (95% CI) of patients who achieved NSAA levels ≥0.1 IU/mL at 72 hours was 64% (47%-82%) in cohort 1a, 91% (84%-97%) in cohort 1b, and 90% (81%-98%) in cohort 1c. At 48 hours, >95% of patients in each cohort (cohort 1a, 97% [91%-100%]; cohort 1b, 99% [96%-100%]; and cohort 1c, 96% [90%-100%]) achieved NSAA levels ≥0.1 IU/mL (Figure 2A). The proportions of patients who achieved NSAA levels ≥0.4 IU/mL following the first treatment course are presented in supplemental Table 2. The mean (interquartile range[25,75]) NSAA levels at 72 hours

Table 1. Demographic and baseline disease characteristics (safety analysis set)

Characteristic	Cohort 1a 25 mg/m^2 MWF (n = 33)	Cohort 1b 37.5 mg/m^2 MWF (n = 83)	Cohort 1c 25/25/50 mg/m^2 MWF (n = 51)	Total (N = 167)
Age, y				
Median (range)	11 (1-24)	8 (1-20)	12 (3-25)	10 (1-25)
<6, n (%)	9 (27)	24 (29)	11 (22)	44 (26)
6-<12, n (%)	9 (27)	34 (41)	14 (27)	57 (34)
12-<18, n (%)	7 (21)	20 (24)	18 (35)	45 (27)
≥18, n (%)	8 (24)	5 (6)	8 (16)	21 (13)
Sex, n (%)				
Male	17 (52)	55 (66)	31 (61)	103 (62)
Race, n (%)				
American Indian or Alaska native	0	0	3 (6)	3 (2)
Asian	1 (3)	5 (6)	1 (2)	7 (4)
Black or African American	3 (9)	11 (13)	8 (16)	22 (13)
White	24 (73)	58 (70)	33 (65)	115 (69)
Multiple	1 (3)	0	0	1 (1)
Not reported	4 (12)	9 (11)	6 (12)	19 (11)
BMI, median (range), kg/m^2	19.9 (13.4-42.6)	17.9 (13.7-30.7)	18.4 (13.8-42.0)	18.4 (13.4-42.6)
BSA, median (range), m^2	1.28 (0.44-2.53)	1.01 (0.56-2.26)	1.29 (0.54-2.43)	1.19 (0.44-2.53)
Primary disease, n (%)				
ALL				
B-ALL	27 (82)	60 (72)	37 (73)	124 (74)
T-ALL	4 (12)	13 (16)	9 (18)	26 (16)
LBL				
B-LBL	0	0	1 (2)	1 (1)
T-LBL	2 (6)	10 (12)	4 (8)	16 (10)
Eligibility criteria met, n (%)				
Grade ≥3 allergic reaction to an *Escherichia coli*–derived asparaginase*	27 (82)	75 (90)	44 (86)	146 (87)
Silent inactivation	3 (9)	3 (4)	1 (2)	7 (4)
Allergic reaction with inactivation	3 (9)	5 (6)	6 (12)	14 (8)

Patients received various ALL/LBL treatment protocols, including (but not limited to) Children's Oncology Group AALL0434, AALL0932, AALL1131, AALL1231, AALL1731, and AALL1732, as well as DFC16-001 and TOT17.

B-ALL, B-cell ALL; B-LBL, B-cell LBL; BMI, body mass index; BSA, body surface area; T-ALL, T-cell ALL; T-LBL, T-cell LBL.

*All patients in part A received pegaspargase before entering the study.

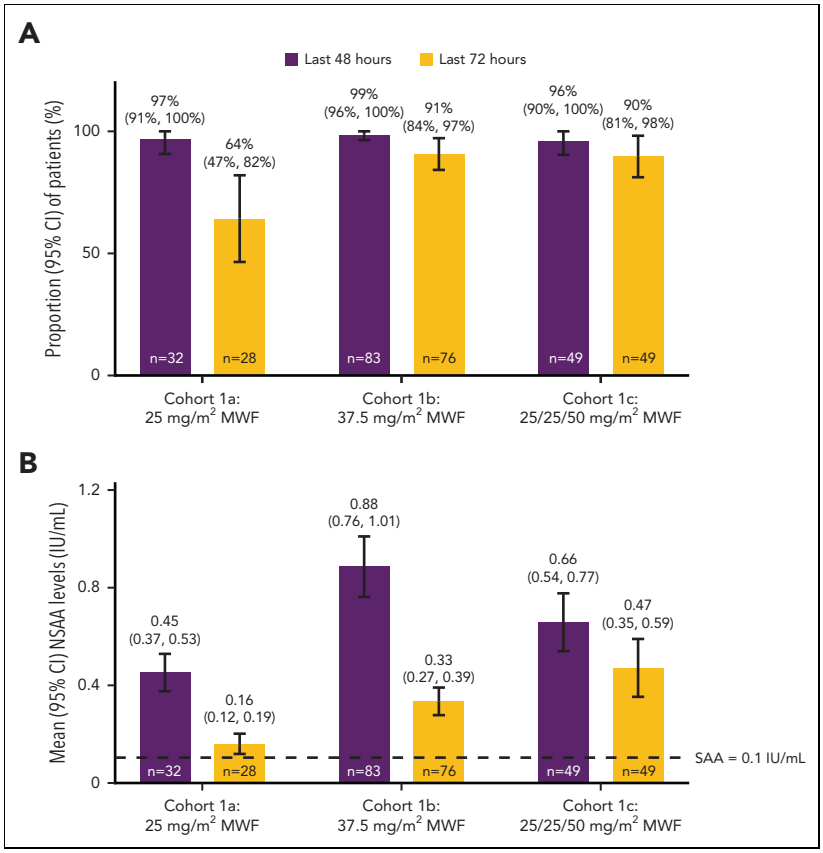

Figure 2. NSAA levels in the first treatment course by cohort. (A) Proportion of patients achieving NSAA levels ≥0.1 IU/mL in the first treatment course. Error bars represent 95% CIs calculated by the Wald method. (B) Mean NSAA levels for evaluable patients in the first treatment course. Error bars represent 95% CIs.

were 0.16 (0.09-0.23) in cohort 1a, 0.33 (0.17-0.41) in cohort 1b, and 0.47 (0.17-0.59) in cohort 1c. At 48 hours, mean NSAA levels were 0.45 (0.27-0.65) in cohort 1a, 0.88 (0.47-1.09) in cohort 1b, and 0.66 (0.33-0.89) in cohort 1c. Figure 2B shows that the mean (95% CI) NSAA levels (IU/mL) during the first treatment course at the last 72 and 48 hours were ≥0.1 IU/mL in all cohorts.

PopPK modeling and simulations

The clinical efficacy of JZP458 was demonstrated by a combination of observed data and modeled results, which included observed NSAA levels at the protocol-specified time points and PopPK modeling and simulation results. The PopPK model that best described the PK (based on SAA) of JZP458 following IM administration was a 1-compartment IM model with mixed-order absorption and linear elimination, with body surface area included as an allometric covariate on JZP458 SAA clearance and volume of distribution, accompanied with self-reported race (ie, Black/African American) and disease subtype (ie, T-cell ALL) as categorical covariates on JZP458 SAA clearance. This model indicated that the simulated proportion of patients achieving NSAA ≥0.1 IU/mL exceeded 90% in both Black/African American and non-Black/African American patients, suggesting that no clinically significant difference would be expected in patients following the proposed body surface area–based dosing. Therefore, no dose modification is recommended on the basis of ethnicity, including African American patients.

Using this PopPK model, simulations suggested that when JZP458 is administered IM at 25/25/50 mg/m^2 MWF, 92.1% (95% CI, 90.9%-93.3%) of patients were expected to achieve the last 72-hour NSAA levels ≥0.1 IU/mL and 93.8% (95% CI, 92.7%-94.9%) of patients were expected to achieve the last 48-hour NSAA levels ≥0.1 IU/mL.

Asparagine depletion

Depletion of plasma asparagine was observed after IM JZP458 administration for all patients in all dosing cohorts. In course 1, mean predose (baseline) L-asparagine concentrations ranged from 7.59 to 11.32 μg/mL for all dose levels and schedules, consistent with literature-reported values.[10] For all cohorts following IM JZP458 administration, mean plasma asparagine levels rapidly declined from predose levels to levels below or near the assay lower limit of quantitation (0.025 μg/mL); reduced plasma levels lasted throughout the treatment duration of course 1 up to predose 6, when the last sample was collected (Figure 3). Plasma asparagine levels over time were similar across all 3 dosing schedules (ie, MWF vs Wednesday/Friday/Monday vs Friday/Monday/Wednesday). Four patients had transient low-level increases in plasma asparagine (cohort 1a, 3 patients; and cohort 1b, 1 patient).

Safety

A total of 124 (74.3%) patients experienced treatment-related AEs, and 86 (51.5%) patients experienced grade 3/4 treatment-related AEs (Table 2). The most common

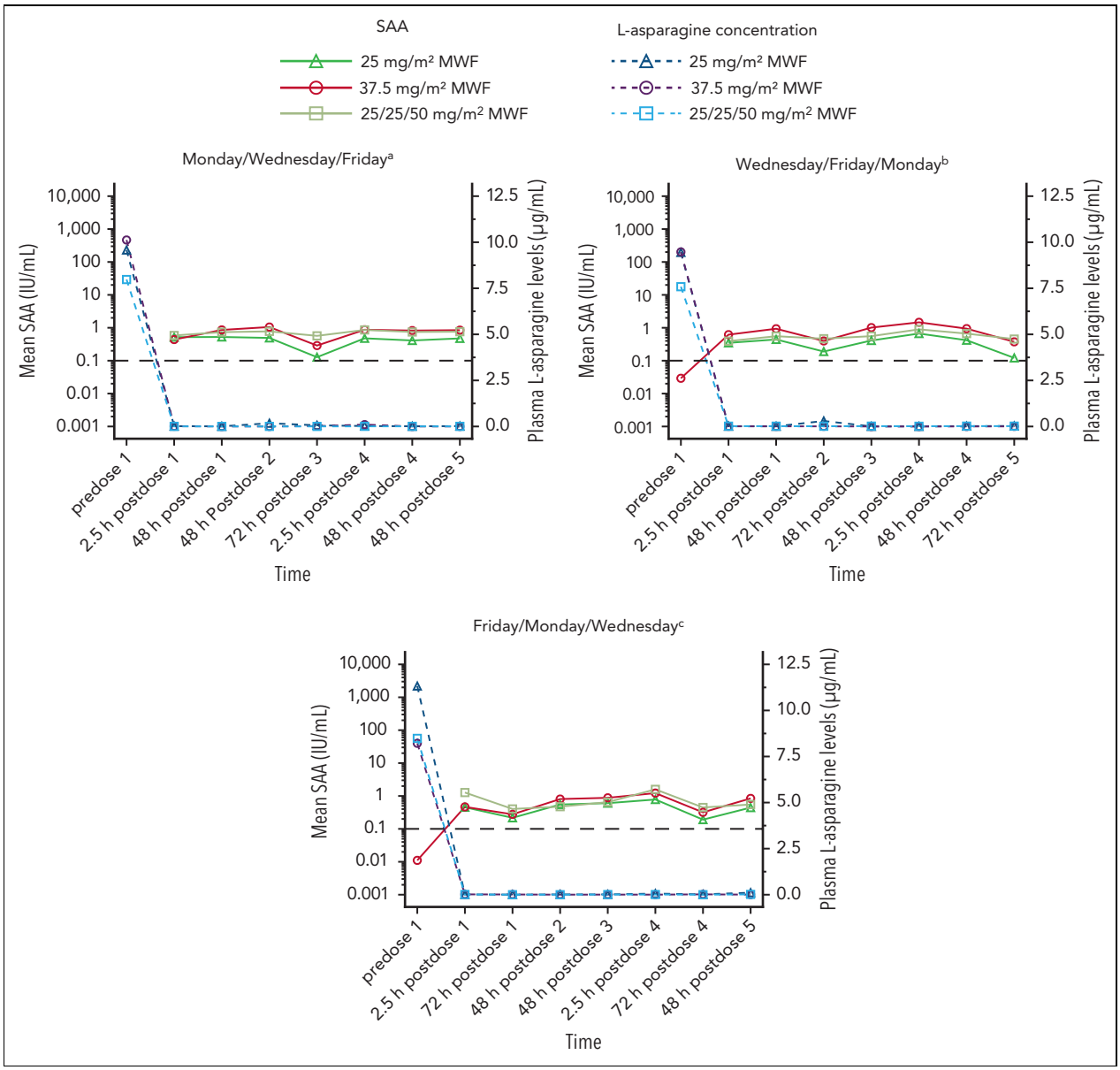

Figure 3. Mean SAA-time profiles and corresponding mean plasma L-asparagine levels in the first treatment course by cohort and dosing schedule. The lower limit of quantitation (LLOQ) values were as follows: SAA = 0.0350 IU/mL; L-asparagine = 0.0250 µg/mL. Values below the LLOQ were graphed as 0 on the linear scale or omitted from the semilogarithmic scale. Only SAA is graphed on a semilogarithmic scale. [a]For cohort 1a, the sample size for mean SAA levels and plasma asparagine levels ranged from 8 to 12 patients for all time points. For cohort 1b, the sample size ranged from 15 to 22 patients for all time points. For cohort 1c, the sample size ranged from 17 to 19 patients for all time points. [b]For cohort 1a, the sample size for mean SAA levels and plasma asparagine levels was 7 patients for all time points. For cohort 1b, the sample size ranged from 27 to 32 patients for all time points. For cohort 1c, the sample size ranged from 18 to 23 for all time points. [c]For cohort 1a, the sample size for mean SAA levels and plasma asparagine levels ranged from 6 to 8 patients for all time points. For cohort 1b, the sample size ranged from 23 to 29 patients for all time points. For cohort 1c, the sample size ranged from 6 to 8 patients for all time points.

nonhematologic grade 3/4 treatment-related AEs were febrile neutropenia (9.0%), increased alanine aminotransferase (7.8%), and nausea (5.4%) (Table 3). In total, 21 (12.6%) patients discontinued JZP458 because of treatment-related AEs: pancreatitis (6.0%), allergic reactions (5.4%), including anaphylaxis (1.8%), increased alanine aminotransferase (0.6%), and hyperammonemia (0.6%). Treatment-emergent AEs that led to death were sepsis (cohort 1a, n = 1), aspiration pneumonia (cohort 1b, n = 1), and multiorgan failure (cohort 1b, n = 1), none of which was deemed to be related to JZP458 treatment.

Treatment-related AEs of special interest included allergic reactions, pancreatitis, and thrombosis; incidence by preferred term is presented in supplemental Table 4. Allergic reactions related to JZP458 were observed in 16 (9.6%) patients, including 3 (1.8%) with anaphylactic reaction (Table 3). Incidence of grade 3/4 treatment-related AEs of special interest among all cohorts were as follows: allergic reactions (5.4%), pancreatitis (6.0%), and thrombosis (1.2%). Treatment-related AEs of hepatotoxicity, predominately elevation of liver enzymes, increased bilirubin, and/or ammonia of any grade, occurred in 33 (19.8%) patients

Table 2. Summary of adverse events

Type of AE	Cohort 1a: 25 mg/m^2 MWF (n = 33)	Cohort 1b: 37.5 mg/m^2 MWF (n = 83)	Cohort 1c: 25/25/50 mg/m^2 MWF (n = 51)	Total (N = 167)
Any treatment-related AE	21 (64)	66 (80)	37 (73)	124 (74)
Any treatment-related grade 3/4 AE	14 (42)	46 (55)	26 (51)	86 (51)
Any treatment-related serious AE	5 (15)	28 (34)	12 (24)	45 (27)
Any treatment-related AE leading to study drug discontinuation	2 (6)	14 (17)	5 (10)	21 (13)
Any treatment-related AE leading to death	0	0	0	0

Data are given as number (percentage) of patients.

(supplemental Table 5). Treatment-related hypertriglyceridemia occurred in 12 (7.2%) patients. Grade 4 hypertriglyceridemia, which was deemed related to JZP458, was reported in 1 (3.0%) patient in cohort 1a and 1 (2.0%) patient in cohort 1c.

Discussion

Incorporation of L-asparaginase into multiagent regimens has been of significant importance in improving outcomes of children and adolescents with ALL, and omission of asparaginase (or low/nondetectable serum levels after its administration) may lead

Table 3. Most commonly reported (≥10% in any cohort) nonhematologic treatment-related adverse events*

	Cohort 1a: 25 mg/m^2 MWF (n = 33)		Cohort 1b: 37.5 mg/m^2 MWF (n = 83)		Cohort 1c: 25/25/50 mg/m^2 MWF (n = 51)	
Type of AE	All grades	Grade 3/4	All grades	Grade 3/4	All grades	Grade 3/4
Nausea	7 (21)	1 (3)	20 (24)	6 (7)	13 (25)	2 (4)
Vomiting	7 (21)	0	22 (27)	3 (4)	10 (20)	1 (2)
ALT increased	2 (6)	2 (6)	14 (17)	8 (10)	8 (16)	3 (6)
Decreased appetite	3 (9)	1 (3)	12 (14)	3 (4)	8 (16)	1 (2)
Fatigue	3 (9)	1 (3)	17 (20)	0	2 (4)	0
AST increased	2 (6)	0	12 (14)	4 (5)	3 (6)	0
Abdominal pain	2 (6)	0	9 (11)	2 (2)	6 (12)	0
Febrile neutropenia	2 (6)	2 (6)	11 (13)	11 (13)	2 (4)	2 (4)
Hyperglycemia	3 (9)	1 (3)	5 (6)	2 (2)	6 (12)	2 (4)
Treatment-related AEs of special interest						
Allergic reaction†	2 (6)	2 (6)	11 (13)	6 (7)	3 (6)	1 (2)
Pancreatitis‡	0	0	6 (7)	6 (7)	6 (12)	4 (8)
Thrombosis§	0	0	2 (2)	2 (2)	0	0

Data are given as number (percentage) of patients.

ALT, alanine aminotransferase; AST, aspartate aminotransferase.

*Treatment-related AEs were reported as *Medical Dictionary for Regulatory Activities* (version 22.1) preferred terms.

†Includes drug hypersensitivity, anaphylactic reaction, hypersensitivity, infusion-related reaction, rash maculopapular, rash, urticaria, and rash erythematous.

‡Includes pancreatitis and acute pancreatitis. Reporting of pancreatitis by the preferred terms "pancreatitis" or "acute pancreatitis" was assigned by the investigator. However, there was no clear distinction between the 2 preferred terms.

§Includes superior sagittal sinus thrombosis, pulmonary embolism, and jugular vein thrombosis.

to higher risk of relapse and, in patients with recurrent disease, a poorer response to reinduction therapy.[11–13] *E coli*–derived asparaginases (particularly pegylated formations) are typically used in frontline ALL protocols. Asparaginases derived from *E chrysanthemi* have a distinct immunologic profile and have long been the only option available to patients unable to receive *E coli*–derived formulations because of hypersensitivity or silent inactivation. In recent years, switching from an *E coli*–derived asparaginase to an *Erwinia*-derived preparation has proved challenging because of manufacturing issues with native asparaginase *E chrysanthemi* (Erwinaze/Erwinase), leading to global shortages.[14] Because of this critical unmet medical need, JZP458 was developed as a novel asparaginase product to provide a reliable treatment option for patients who develop hypersensitivity to *E coli*–derived asparaginases. The JZP458 clinical program, including the pivotal phase 2/3 AALL1931 trial, was conducted in close collaboration with the Children's Oncology Group and the FDA under the accelerated RTOR program.

The clinical effectiveness of asparaginase is thought to be based on adequate depletion of asparagine[3,15,16]; however, accurate measurement of asparagine levels is technically challenging and not practical in the clinical setting. Thus, serum asparaginase activity serves as a surrogate marker for asparagine depletion in clinical trials and for patient care.[3,4] Although one study of pegylated *E coli*–derived asparaginase has suggested that a higher level of asparaginase activity (≥0.4 IU/mL) may be needed for complete asparagine depletion, particularly in the cerebrospinal fluid,[17] the preponderance of the literature suggests the NSAA threshold of ≥0.1 IU/mL as the target to ensure therapeutic benefit from asparaginase therapy.[3,15,16] Therefore, an NSAA threshold of ≥0.1 IU/mL was used to define the primary and key secondary efficacy end points in the JZP458 AALL1931 study, whereas an NSAA threshold of ≥0.4 IU/mL was explored as a secondary end point.

An interim analysis of data from the first 102 patients enrolled in AALL1931 (primarily in cohorts 1a and 1b), in conjunction with PopPK modeling and simulations, suggested that 94% (95% CI, 93%-95%) of patients would be expected to maintain NSAA levels ≥0.1 IU/mL at 48 hours at 25 mg/m^2 with 7 doses per 2-week course.[18] These data, along with interim safety data, were considered sufficient by the FDA to support the approval of JZP458 at 25 mg/m^2 every 48 hours under the RTOR program, providing timely access to an *Erwinia*-derived asparaginase to patients in need. The FDA accepted the observed and simulated data to meet the required efficacy target as the basis for its decision. Data from all 167 IM patients enrolled in part A of AALL1931 were provided to the FDA to pursue a label update to include the IM dosing regimen with 25/25/50 mg/m^2 MWF, which may be the preferred option at some institutions that cannot easily administer asparaginase in the outpatient setting over the weekend.

Herein, we report the results for all 167 patients enrolled in part A of AALL1931, including 51 patients in cohort 1c. Results from this follow-up analysis demonstrate that the IM dosing regimen of 25/25/50 mg/m^2 MWF (cohort 1c), which intentionally used a higher Friday dose to improve the 72-hour SAA coverage, is efficacious and tolerable, based on observed data and model-based simulations as well as the observed safety profile. The observed data indicated similar proportions of patients achieved 72-hour NSAA levels ≥0.1 IU/mL in cohort 1c (90%) and cohort 1b (91%), although the mean SAA levels at the last 72 hours were higher in cohort 1c than in cohort 1b (0.47 [95% CI, 0.35-0.59] IU/mL vs 0.33 [95% CI, 0.27-0.39] IU/mL). However, the study was not powered to compare results among cohorts. When the observed data were used to refine the PopPK model, simulations indicate that 92.1% (95% CI, 90.9%-93.3%) of patients are expected to achieve the last 72-hour NSAA levels ≥0.1 IU/mL with JZP458 administered IM at 25/25/50 mg/m^2 MWF. PopPK modeling and simulation has several important advantages in that it uses pooled data from all patients, all dose levels, all time points, and across all courses, and it uses continuous rather than categorical data, resulting in more precise estimation of NSAA levels in a large population, as manifested by the tight 95% CI.

The study was not designed to test for statistically significant differences between safety profiles among cohorts. However, the totality of observed safety data from cohort 1c appeared similar to the safety data from cohorts 1a (25 mg/m^2 MWF) and 1b (37.5 mg/m^2 MWF) and were consistent with what has been described for other asparaginases.[1,2,19–21] Limitations of this study include the single-arm design. In addition, at the data cutoff date for the results presented in this article, some patients had not completed treatment; therefore, the complete safety follow-up data will need to be reported in a future article.

Conclusions

IM JZP458 using the dosing regimen of 25/25/50 mg/m^2 MWF is efficacious, is tolerable, and achieves NSAA levels ≥0.1 IU/mL at both 48 and 72 hours in the vast majority of patients. The safety profile of JZP458 is consistent with what has been described for other asparaginase products.[1,2,19–21] Data from all 167 patients treated with IM JZP458 in part A of AALL1931 were provided to the FDA to support a label update to include the IM dosing regimen of 25/25/50 mg/m^2 MWF, in supplement of the approved dosing of 25 mg/m^2 every 48 hours. Future studies are needed to determine the impact of JZP458 on patient experience and outcomes. These dosing regimens optimize SAA coverage, provide flexibility, and bring alignment with many pediatric oncology protocols throughout the world. More importantly, with its reliable manufacturing process, and the efficacy and safety demonstrated in AALL1931, JZP458 addresses one of the most significant drug shortages impacting the care of patients with ALL/LBL.

Acknowledgments

This study was conducted in collaboration with the Children's Oncology Group. The authors thank all investigators who contributed to this project, the patients who participated in this study, the staff members at the study sites, the study data review committee, and the staff members involved in data collection and analyses. Medical writing and editorial support were provided by Austin Horton of Cello Health Communications/SciFluent Communications and were financially supported by Jazz Pharmaceuticals.

Authorship

Contribution: L.M., M.L.L., M.R.C., R.I., J.A.S., T.L., E.A.R., and R.E.R. conceived and designed the study; L.M., M.L.L., M.R.C., T.L., E.A., M.Z., S.A., J.A.S., L.B.S., E.A.R., and R.E.R. collected and assembled data. All authors performed data analysis and interpretation, wrote the manuscript, and provided final approval of the manuscript and are accountable for all aspects of the work.

Conflict-of-interest disclosure: L.M. served on an advisory board and speakers bureau for Jazz Pharmaceuticals. M.R.C., T.L., E.A., M.Z., S.A., and R.I. are employees of and hold stock ownership and/or stock options in Jazz Pharmaceuticals. J.A.S. was an employee of Jazz Pharmaceuticals at the time of the study and holds stock ownership and/or stock options in Jazz Pharmaceuticals. L.B.S. served on scientific advisory boards for Jazz Pharmaceuticals and Servier Pharmaceuticals. E.A.R. received institutional research funding from Pfizer and serves on a Data and Safety Monitoring Board for Bristol Myers Squibb. R.E.R. served on advisory boards for Jazz Pharmaceuticals and Servier Pharmaceuticals. The remaining authors declare no competing financial interests.

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Footnotes

Submitted 22 June 2022; accepted 6 September 2022; prepublished online on *Blood* First Edition 15 September 2022. https://doi.org/10.1182/blood.2022016923.

Initial results of this study were presented at the 63rd American Society of Hematology Annual Meeting and Exposition, Atlanta, GA, 11 to 14 December 2021, poster 2307; results of this study were also presented at the American Society of Clinical Oncology Annual Meeting, Chicago, IL, 3 to 7 June 2022, abstract 7001.

All relevant data are provided with the article and supporting files. Jazz has established a process to review requests from qualified external researchers for data from Jazz-sponsored clinical trials in a responsible manner that includes protecting patient privacy, assurance of data security and integrity, and furthering scientific and medical innovation. Additional details on Jazz Pharmaceuticals data sharing criteria and process for requesting access can be found at: https://www.jazzpharma.com/science/clinical-trial-data-sharing/.

The online version of this article contains a data supplement.

There is a *Blood* Commentary on this article in this issue.

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